

## Chapter 13

### Complications of Liver Disease

**A1a. Hold a research workshop on improvement and standardization of clinical measurements of cirrhosis and portal hypertension.** The NIH is organizing a workshop entitled “Measurement of Hepatic Vein Pressure Gradient: Role in Management of Portal Hypertension” to be held on June 16-17, 2006 with 17 invited speakers. (0%)

**A1b. Define whether N-acetylcysteine is beneficial in acute liver failure.** Two prospective randomized controlled trials of N-acetylcysteine (NAC) for non-acetaminophen induced acute liver failure have received NIH funding. A trial in adults has accrued 140 patients; a trial in children has just begun. (20%)

**A2. Better define the natural history of hepatopulmonary syndrome and whether early detection is beneficial.** An NIH funded National Network on Hepatopulmonary Syndrome has been initiated. The presence of HPS does not appear to have a detrimental effect on the outcome of liver transplantation (Kim HY. *Trans Proc* 2004;36:2762-3). (10%)

**A3a. More fully elucidate the pathophysiology of portal hypertension.** Portal hypertension appears to be mediated in part by deficiency in nitric oxide activity the cause of which has been partially elucidated in rodent models (Laleman W. *Hepatology* 2005;42:1382). Hydrogen sulfide (H<sub>2</sub>S) may independently help regulate portal pressure and be deficient in cirrhosis (Fiorucci S. *Hepatology* 2005; 42:539). The hyperdynamic splanchnic circulation of cirrhosis is mediated in part by vascular endothelial growth factor (VEGF), a potent angiogenesis signaling molecule (Fernandez M. *J Hepatol* 2005;43:6). These findings provide potential targets for more physiologically based therapies for portal hypertension. (10%)

**A3b. Better characterize the cause of increased susceptibility to bacterial infections in cirrhosis.** Elucidation of the basic mechanisms by which patients with cirrhosis are at increased risk for infections might lead to means of prevention. Infections remain a major cause of morbidity and mortality in patients with cirrhosis. (0%)

**B1. Define optimal nonspecific approaches to management of hepatic encephalopathy, hepatorenal syndrome, refractory ascites, prevention of bacterial infection, and coagulopathy in patients with cirrhosis.** A clinical trial of terlipressin vs placebo for treating hepatorenal syndrome in cirrhotic patients is nearing completion. (0%)

**B2a. Define whether hypothermia is beneficial in acute liver failure for management of cerebral edema.** An investigator-initiated trial of hypothermia for acute liver failure has been planned, but has yet to be funded. (0%)

**B2b. Define natural history and identify predictors of development and growth of varices.** A recent NIH-funded study has shown that the level of portal pressure is predictive of variceal growth and bleeding and that a fall in portal pressure

indicates a better prognosis (Groszmann R. *N Engl J Med* 2005; 353:2254-61). (20%)

**B3a. Identify small molecule targets that would lead to better control of portal hypertension at different stages of disease.** No new agents for portal hypertension have been approved for use. *In vitro*, high-throughput screening of small molecules is encouraged by the NIH Roadmap through the trans-NIH RFA on “Assay Development for High Throughput Molecular Screening” (RM-05-011). (0%)

**B3b. Develop a noninvasive means of measuring portal pressure.** The NIH-sponsored research workshop on “Measurement of Hepatic Vein Pressure Gradients: Role in Management of Portal Hypertension” planned for June 2006 will include presentations on noninvasive approaches. Efforts to develop noninvasive means to assess portal pressure are encouraged by the program announcement on “Noninvasive Methods for Diagnosis and Progression” (PA-04-088). (0%)

**C1a. Elucidate the optimal approach to manage patients with varices that have not bled (primary prevention).** A recent study on prevention of varices in patients with cirrhosis showed minimal effects of beta blocker therapy (Groszmann R. *N Engl J Med* 2005;353:2254), while a second study showed slowing of growth of small varices (Merkel C. *Gastroenterology* 2004;127:476). Further studies are warranted to compare band ligation, beta blocker therapy, and more innovative approaches. (10%)

**C1b. Define whether monitoring portal pressure (HVPG) improves management of patients with chronic liver disease.** The workshop on “Measurement of Hepatic Vein Pressure Gradient: Role in Management of Portal Hypertension” to be held on June 16-17, 2006 will deal directly with this issue. (0%)

**C2a. Develop a noninvasive means to assess hepatic regeneration and reserve in liver failure.** Efforts to assess regeneration and reserve function in cases of liver failure are encouraged by NIH-funded initiatives on “Development of Disease Biomarkers” (PA-05-098) and “Noninvasive Methods for Diagnosis and Progression” (PA-04-088). (0%)

**C2b. Develop and evaluate better drugs for portal hypertension.** Recent animal studies have been conducted and human studies are planned to evaluate new drugs that are nitric oxide-releasing derivatives of ursodeoxycholic acid for treating portal hypertension. (10%)

**C3a. Develop an artificial or bioartificial hepatic support and demonstrate that it prolongs survival in acute liver failure.** Several industry groups are currently pursuing the development of artificial or bioartificial liver support devices. An NIH-sponsored meeting on acute liver failure that will focus on progress in liver support devices is being planned for December 2006. (0%)

**C3b. Develop noninvasive means to screen for large varices.** Studies are ongoing in this area, focusing on developing noninvasive indicators of varices size, such as

platelets and splenic size. Development of noninvasive screening tests for varices are encouraged in the program announcement on “Noninvasive Methods for Diagnosis and Progression” (PA-04-088). (0%)

Figure 15. Estimated Progress on Complications of Liver Disease Research Goals, 2005 (Year 1)

